REMARKS CONCERNING THE AMENDMENTS

The above amendments have been made in an effort to more clearly define a narrower scope of the present invention. Claims have been combined to place them in condition for allowance. The new independent claims comprise the allowable subject matter and all claims, including intervening limitations, from which they depend. Other allowable claims now depend from these amended independent claims.

Claims 5 and 6 have been amended to recite that property changes occur in "cell chemistry" as opposed to measuring physical property changes in the cell mass itself. This distinguishes even further from process done by Weiss, Wald and Judd, where only the cells themselves are observed with respect to physical attributes such as volume.

Other Amendments are clearly editorial in nature, renumbering claims and correcting antecedent references.

SUMMARY OF THE REJECTIONS

1) Claims 1-9, 13-16, 24-28, 30-43 and 47-53 have been rejected under 35 USC 103(a) as unpatentable over Weiss et al. (U.S. Patent No. 5,980,885) in view of Wald (U.S. Patent No. 6,181,134).

The rejection is believed to be fairly summarized as asserting (without conceding the accuracy of the assertions) that:

Weiss et al. teaches a method of treating a neurodegenerative disease comprising the steps of:

a) Transplanting cultured stem cell into the body (Column 10, lines 44-51 and column 11, lines 43-65);

b) Detecting survival of transplanted graft through various imaging modality, including MR and CT scanning;

c) Ranges of transplanted cells (as opposed to complete organs) include cell colonies and cells grown in cultures prior to implantation (Column 1, lines 40-60);

d) However, Weiss does not elaborate on the particular characteristics used in observing graft survival;

e) Wald teaches using MR to detect NAA, lactate and neurotransmitter levels in indicating neuronal metabolism and viability (Column 5, lines 15-16;

f) From these asserted teachings it is asserted to be obvious to one skilled in the art under 35 USC 103(a) to combine these teachings so that the success of the (cell) transplantation in the long term can be assessed.

2) Claims 1, 3, 6, 10-12 and 27-29 have been rejected under 35 USC 103(a) as obvious over Weiss (et al., as cited above) in view of Judd (U.S. Patent No. 5,910,112).

The teachings of Weiss are again repeated. It is then asserted in this rejection that although Weiss does not teach the specific techniques recited, such as the Na-23 levels, Judd teaches an MR imaging device for observing viability of heart cells, non-destructively monitoring Na-23 levels. It is asserted to have been obvious to one skilled in the art to use the specific techniques of Na-23 monitoring taught by Judd in the process of Weiss to monitor long-term success of cell transplantation.

RESPONSE TO THE REJECTIONS

1) Claims 1-9, 13-16, 24-28, 30-43 and 47-53 have been rejected under 35 USC 103(a) as unpatentable over Weiss et al. (U.S. Patent No. 5,980,885) in view of Wald (U.S. Patent No. 6,181,134).

The sole teachings of Weiss with respect to examining for cell survival are:

> "Survival of the graft in the living host can be examined using various non-invasive scans such as computerized axial tomography (CAT scan or CT scan), nuclear magnetic resonance or magnetic resonance imaging (NMR or MRI) or more preferably positron emission tomography (PET) scans. Post-mortem examination of graft survival can be done by removing the neural tissue, and examining the affected region macroscopically, or more preferably using microscopy. Cells can be stained with any stains visible under light or electron microscopic conditions, more particularly with stains which are specific for neurons and glia. Particularly useful are monoclonal antibodies which identify neuronal cell surface markers such as the M6 antibody which identifies mouse neurons. Most preferable are antibodies which identify any neurotransmitters, particularly those directed to GABA, TH, ChAT, and substance P, and to enzymes involved in the synthesis of neurotransmitters, in particular, GAD. Transplanted cells can also be identified by prior incorporation of tracer dyes such as rhodamine- or fluorescein-labelled microspheres, fast blue, bisbenzamide or retrovirally introduced histochemical markers such as the lac Z gene which produces beta galactosidase." (Column 23, lines 41-62); and

> "Neuromyelitis optica is a condition involving demyelination of principally the spinal cord and optic nerve. Onset is usually acute and in 50% of the cases death occurs within months. The severity

> of demyelination as well as lesion sites can be confirmed by magnetic resonance imaging (MRI).
> "Neural stem cell progeny are prepared from fetal human tissue by the methods of Example 9 or 14. Cells are stereotactically injected into the white matter of the spinal cord in the vicinity of plaques as visualized by MRI. Cells are also injected around the optic nerve as necessary. Booster injections may be performed as required." (Example 16; columns 41 and 42).

To one of ordinary skill in the art it is absolutely clear from the mere general reference to MRI and the somewhat more specific statement in Example 16 that MRI is being used solely as a direct visualization process to observe cell mass. Weiss teaches direct observation of cell mass to see if cells have attached and if the region exhibits visually observable growth. This is the most simplistic possible instruction that does little more than look directly at the cell mass to see if it is there. This is precisely the crude observational technique that the present invention is a direct improvement over.

By directly viewing cell mass increase or deterioration, all that can be observed is some visual evidence that the region has gotten larger or smaller in mass. This provides a gross intuitive finding that some cells are adding to the observed mass or that cells are being lost. This observation can also not easily distinguish between residual dead cells, scar tissue or any other mass that has accumulated in the area. This is absolutely clear from the minimalist description of observation in the specification and the somewhat more specific reference to confirming lesion sites (which can only be visually observed, as the lesion would not alter blood chemistry). Therefore, the teaching of Weiss is effectively only that one can look at the transplant site to observe cell mass and cell volume, and one can even perform a post mortem examination to observe 'survivability.' (Column 23, lines 41-62).

Given this weak introductory teaching of Weiss to observe survival of the graft (as opposed to cell survival on a cellular level), the Wald reference has a significant burden in providing a motivating teaching of the differences between the teachings of Weiss and the claimed invention.

The teachings of Wald are quite distinct from the objectives of Weiss et al. Wald teaches a unique imaging procedure using MRI to effect better resolution of mapping of chemical distributions within an organ. Specifically, a general description of the objective of Wald would be:

> "The invention features a method for imaging the distribution of a marker compound in a sample, such as living tissue, using magnetic resonance imagining. The method includes i) exciting the tissue to generate magnetic resonance signals, including signals corresponding to the marker compound and ii) suppressing non-marker compound magnetic resonance signals using band selective inversion with gradient dephasing and chemical shift selective pre-excitation. The method can further include iii) encoding the remaining marker compound signal using conventional readout and phase encoding gradients. Examples of marker compounds include n-acetyl aspartic acid, citrate, choline, phosphocreatine, and lactate in mammalian tissue." (Summary of the Invention, column 1, lines 52-64).

Wald is observing the distribution of specific chemicals within an MRI slice or slices of an organ. There is a critical failure in the proposed combination of the references that establishes a complete failure in the required motivation needed to establish obviousness.

There is no teaching of observing chemical changes (indicated by non-invasive means such as MRI) to indicate cell survivability. Wald provides a mere chemical mapping process, with no intent or indication of its indication of changes in cell performance. As Weiss teaches mere gross observation of mass, and Wald does not suggest a quantitatively analytic process to observe changes by "sensing a property in the region" of transplantation as recited in the claims, there is no motivation to one skilled in the art to combine the two distinct processes.

It is well established that the PTO:

> "...bears the burden of establishing a prima facie case of obviousness based on the prior art...[the Examiner] can satisfy this burden only by showing some objective teaching in the prior art...would lead that individual to combine the relevant teachings of the prior art." (*In re Fritch*, 23 USPQ2d 1780, Fed. Cir. 1992)

It is also necessary that there be a reason provided by the prior art that motivates the skilled artisan to make the specific alteration between prior art references and the invention.

> "Where, as here, nothing of record plainly indicates that it would have been obvious to combine previously separate process steps into one process, it is legal error to conclude that a claim to that process is invalid under 103." (*Fromson v. Advance Offset Plate, Inc.*, 225 USPQ 22, Fed. Cir. 1985)

> "The fact that a prior art device could be modified so as to produce the claimed device is not a basis for an obviousness rejection unless the prior art suggested the desirability of such a modification." (*In re Gordon*, 221USPQ 1125, Fed Cir. 1984) See also *In re Laskowski*, 10 USPQ2d 1397, Fed Cir. 1989.

Of additional importance to the indication of failure of the combination of references is that neither Weiss nor Wald suggests that properties themselves (as opposed to volume per se) are indicative of cell survivability. Without that nexus to the process of the present invention, this combination of references fails to establish the obviousness of the fundamental process claimed, and the success of that process. As there is no teaching of measurement of properties in the region to determine cell viability (and specifically in blood chemistry, in claims 6 and 7), there is a fundamental failure to teach the present invention.

Weiss clearly does not attempt to measure by MRI any property related specifically to cell survivability, merely observing cell mass. Wald at most observes chemistry distribution within an organ (not in implanted cells) and his stro9ngest assertion of specific utility is in Example 4 where it is stated "This technique is useful for applications where more than one slice through the anatomy of interest is needed to visualize the pathology of the organ." That is not an indication of the desirability of or motivation towards measuring localized properties to determine call viability after implantation.

The rejection is clearly in error and must be withdrawn.

2) Claims 1, 3, 6, 10-12 and 27-29 have been rejected under 35 USC 103(a) as obvious over Weiss (et al., as cited above) in view of Judd (U.S. Patent No. 5,910,112).

Judd does not use MR to measure a property indicative of cell survivability and cell performance for natural events. What Judd does is to use MR imaging with an artificial chemical addition and checks the performance of that tissue (particularly with respect to its perfusion or chemical transmission of the artificial additive) under MR. It does not attempt to observe a change in cell performance properties in the region. As is clearly shown in Example 3:

> "In- Vivo Procedures--New Zealand White Rabbit were anesthetized with intramuscular ketamine/xylazine (50 mg/kg and 2.5 mg/kg respectively), intubated, and mechanically ventilated. A catheter was placed in the femoral artery to monitor systemic pressure. A left thoracotomy was performed at the fifth intercostal space. A deflated 2-mm angioplasty balloon catheter was loosely asutured around an anterior branch of the left coronary artery. An epicardial marker filed with saline was placed over the territory perfused by the artery, and a catheter was placed in the left atrium for injection of fluorescent microspheres (15 microns, Molecular Probes). The chest was then closed in two layers, the rabbits were placed prone on a 5-cm diameter double-resonant ^{23}Na -^{1}H surface RF coil, and placed in the magnet. Using this approach, coronary artery occlusion and reperfusion could be performed closed-chest in the magnet by inflation ad deflation of the ballon.
>
> "Femoral artery pressure was used for cardiac gating. Double-oblique, short or long-axis ^{1}H images were first acquired using the epicardial marker to identify the to-be-infracted territory. The RF coil was then tuned to the .sup.23 Na frequency and a control ^{23}Na frequency and a control ^{23}Na image was acquired at the same location. ^{23}Na imaging parameters were: imaging time 11 minutes; 16 phase encodes/cardiac cycle (gated to end-diastole); TE 4.6 ms; TR 13 ms; NAIG+256: matrix size+256X128 voxel size 1.25X2.5X6 mm.-Heart rate in these anesthetized rabbits was approximately 180 BPM. A control set of

microspheres was injected into the left atrium. The balloon catheter was then inflated to produce coronary artery occlusion for 40 minutes, a second set of microspheres injected, and another .sup.23 Na image was acquired. The balloon was then deflated to allow reperfusion, a third set of microspheres injected, and another .sup.23 Na image was acquired. After approximately 60 minutes of reperfusion, a final set of microspheres was injected and a final .sup.23 Na image acquired. The hears were then removed and sectioned at the level of the epicardial marker. One side of the heart was stained with TTC to verify the location and extent of infarction. The other side of the heart was used to obtain tissue samples from infarcted and normal regions for spectroscopic analysis of sodium content (see MR Spectroscopy) and for Microsphere flow determination."

No natural event is observed and no cell viability is identified, merely a measurement of a non-functioning transmission capability from a specific region. **This method is also invasive**, requiring local implantation of a device to perform the test and the administration of local active chemistry. The combination of this procedure with Weiss, even if there were some motivation on the record (which there is not), would not produce the process of these claims. This methodology would require the implantation of a unique material delivery device at a specific location.

Also, the process of Judd is specific to only vascular transplant, not cell implantation. The procedure of Judd is not suggestive of use in the field of cell implantation, especially as perfusion measurements through the 'new tissue' is not indicative of survivability and is not meaningful with respect to transplanted cells. The system of Judd is believed uniquely relevant to only vascular surgery, and is disclosed for only that field of practice.

ADDITIONAL COMMENTS ON PATENTABILITY OF CLAIMS

There is absolutely no suggestion that other claim limitations are taught by the references. The quantitation of cell survivability is not suggested by the references (e.g., see claims 41-43 and 47-48). Claims 50-53 recite that the transplanted, transfected cells have been genetically engineered to express a neurotransmitter, an agonist of a neurotransmitter, a precursor of a transmitter that has neurotransmitter activity, derivative of a neurotransmitter that has neurotransmitter activity, analog of a neurotransmitter that has neurotransmitter activity, or fragment of a neurotransmitter that has neurotransmitter activity.

CONCLUSION

Applicants believe that the application and claims are now in proper order and in condition for allowance. Please direct any inquiries to the undersigned attorney at (952) 832-9090.

Respectfully submitted,

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